Diagnosis and management of status epilepticus: improving the status quo

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Status epilepticus is a common neurological emergency that is characterised by prolonged or recurrent seizures without recovery between episodes and associated with substantial morbidity and mortality. Prompt recognition and targeted therapy can reduce the risk of complications and death associated with status epilepticus, thereby improving outcomes. The most recent International League Against Epilepsy definition considers two important timepoints in status epilepticus: first, when the seizure does not self-terminate; and second, when the seizure can have long-term consequences, including neuronal injury. Recent advances in our understanding of the pathophysiology of status epilepticus indicate that changes in neurotransmission as status epilepticus progresses can increase excitatory seizure-facilitating and decrease inhibitory seizure-terminating mechanisms at a cellular level. Effective clinical management requires rapid initiation of supportive measures, assessment of the cause of the seizure, and first-line treatment with benzodiazepines. If status epilepticus continues, management should entail second-line and third-line treatment agents, supportive EEG monitoring, and admission to an intensive care unit. Future research to study early seizure detection, rescue protocols and medications, rapid treatment escalation, and integration of fundamental scientific and clinical evidence into clinical practice could shorten seizure duration and reduce associated complications. Furthermore, improved recognition, education, and treatment in patients who are at risk might help to prevent status epilepticus, particularly for patients living in low-income and middle-income countries.

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Introduction

Status epilepticus is a life-threatening emergency that is characterised by prolonged or recurrent seizures without recovery between episodes. Prompt treatment can prevent irreversible neuronal injury, morbidity, and mortality. In the past 10 years, advances in status epilepticus include refinements to definitions and classification systems, improvements in conventional, quantitative, and rapid EEG, automated seizure detection, and development of comprehensive assessments to ascertain the cause of the seizure. Regarding treatment, intranasal rescue medications have been developed, class 1 evidence for second-line medications has emerged,[1–4] and novel antiseizure medications and targeted treatment for genetic and neuroinflammatory causes are promising. However, disparities in care persist, particularly between high-income countries (HICs) and low-income and middle-income countries (LMICs), as well as within the LMICs themselves.

In this Review, we describe recent changes in the definition of status epilepticus and discuss developments in epidemiology, pathophysiology, and aetiology. We also describe recent advances in the diagnosis, treatment, and prognosis of status epilepticus. Finally, we highlight the challenges and potential future directions in global care for status epilepticus.

Definition and specific status epilepticus syndromes

In 2015, the International League Against Epilepsy (ILAE) proposed a novel definition of status epilepticus that combines historical definitions based on pathophysiology with definitions that emphasise the need for clinical intervention.[5] In parallel, a diagnostic classification system was proposed with four axes: semiology, cause, EEG correlates, and age.

The updated ILAE definition acknowledges that at a timepoint, t_1, either mechanisms that lead to seizure termination have failed or mechanisms that result in an atypically prolonged seizure have been initiated. Once t_1 is reached, the seizure will persist in the absence of emergency treatment. If this treatment is unsuccessful before a second timepoint, t_2, long-term consequences might occur, including neuronal injury, alternations of neuronal networks, or death. On the basis of observational human studies and experimental animal studies that evaluated the duration of self-limited seizures and the long-term consequences of seizures, t_1 was defined as 5 min for tonic-clonic seizures and 10 min for focal seizures with impaired awareness, and t_2 was defined as 30 min for tonic-clonic seizures and more than 60 min for focal seizures with impaired awareness. For absence status epilepticus, t_1 was defined as 10–15 min and t_2 is unknown.

In addition to t_1 and t_2 in status epilepticus, stages and specific syndromes are also defined in the ILAE criteria on the basis of the duration of the seizures and the treatment response. Early or impending status epilepticus refers to continuous or intermittent seizures lasting longer than 5 min without recovery of consciousness in between seizures. Established status epilepticus defines seizures that do not respond to treatment with first-line benzodiazepines. When seizures continue despite the use of two adequately dosed antiseizure medications (eg, a first-line benzodiazepine and a second-line non-benzodiazepine antiseizure medication), a definition of refractory status epilepticus can be made. Refractory status epilepticus can be further

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classified in the ILAE criteria as responsive to subsequent antiseizure medications or requiring general anaesthesia.[6] Refractory status epilepticus that lasts longer than 24 h despite treatment with anaesthetic agents or that recurs on anaesthetic wean is called super-refractory status epilepticus. New-onset refractory status epilepticus (NORSE) and febrile infection-related epilepsy syndrome (FIRES) are specific status epilepticus syndromes within the definition of refractory status epilepticus in the ILAE criteria.[7] NORSE is a clinical diagnosis for presentations of refractory status epilepticus in a patient without an antecedent diagnosis of epilepsy or another neurological disorder.[8] A subset of patients with NORSE have FIRES, in which a febrile infection precedes the onset of refractory status epilepticus by 24 h to 2 weeks.

Epidemiology

The incidence of status epilepticus depends on the factors used to define it. Relevant factors comprise duration, semiology (ie, convulsive or non-convulsive), geographic location (eg, HICs or LMICs, or rural or urban), age distribution of the population, method of case ascertainment (eg, community or hospital, prospective or retrospective, and clinical or registry), cause, and inclusion and exclusion criteria (eg, exclusion of post-anoxic cases and developmental and epileptic encephalopathies).

In Europe and North America, estimates from observational studies of the incidence of convulsive status epilepticus range between nine per 100 000 people and 40 per 100 000 people per year, with higher rates in children and older adults.[9] For example, the incidence of status epilepticus in older people varies from 15·5 per 100 000 people aged 60–69 years per year to 25·9 per 100 000 people older than 80 years per year.[10,11] In LMICs, the incidence of status epilepticus is generally higher than in HICs, particularly in children in whom the leading cause is infectious diseases (eg, malaria).[9] A prospective population-based study of children with status epilepticus found an incidence of 14·5 per 100 000 people per year.[9] The highest age-specific rate, 51 per 100 000 people per year, was found in infants younger than 1 year.[9]

Regarding racial and ethnicity differences, observational studies have shown status epilepticus to be more common in African American people than in White people, and more common in both African American people and White people than in Asian people and Hispanic people.[12,13] By sex, incidence of status epilepticus has been shown in observational studies to be higher in male individuals than in female individuals, although the rate of recurrence has been observed to be higher in female individuals than in male individuals.[13,14] The underlying causes for these differences in incidence of status epilepticus have not been thoroughly explored, but factors such as access to care, socioeconomic status, cultural disparities, and intrinsic biological factors might contribute to these observed disparities.

Researchers from Finland found that the incidence of status epilepticus requiring intensive care unit (ICU) admission was 3·4 per 100 000 people per year, and the incidence of super-refractory status epilepticus was 0·7 per 100 000 people per year.[15] The incidence of status epilepticus that was terminated by treatment in the community (particularly, non-convulsive status epilepticus) has not been robustly studied.

Pathophysiology

Dynamic processes are at play during the prolonged seizures of status epilepticus, the net effect of which is an atypically extended seizure that persists and places substantial demands on homoeostatic mechanisms. When these mechanisms fail, blood pressure drops, brain perfusion and oxygenation are reduced, and concomitant respiratory and metabolic acidosis occurs.[16] Animal models of status epilepticus, in which seizures are induced by electrical stimulation or administration of a chemoconvulsant, have elucidated molecular and cellular changes that affect the balance between inhibition and excitation of seizure mechanisms.

The changes elucidated in animal models include reduced cellular surface expression of GABA type A receptors due to an increase in the intracellular accumulation of these receptors, an increase in the surface expression of NMDA receptors, and an alteration in the subunit configuration of AMPA receptors.[17] In addition to changes in the surface expression of inhibitory and excitatory receptors, changes in the intracellular and extracellular ionic environment can occur. In animal models, neuronal injury and death have been shown to result from dysregulation of calcium-dependent mechanisms and the build-up of reactive oxygen species.[18] The preponderance of ion shifts contributes to the self-propagation of neuronal excitability and network synchronisation.[19] An example of ion shifts that might occur in status epilepticus is an increase in the intracellular concentration of chloride, resulting from chloride loading and failed extrusion of intracellular chloride because of internalisation of the potassium chloride cotransporter KCC2. As a result, GABAergic signalling can shift from hyperpolarising to depolarising. In such an instance, treatment with GABAergic drugs might have the paradoxical effect of increasing neuronal excitability, with the exact response on the network depending on the cell type and function of the cells in which the chloride has accumulated. In an animal model of status epilepticus, KCC2 activation using a small molecule derived from aminopyridine compounds reduced the intracellular accumulation of chloride and restored the effectiveness of benzodiazepines.[20] Changes in expression of cellular receptors and ionic shifts in chloride suggest potential mechanisms for why status epilepticus might become

refractory to first-line medications such as benzodiazepines. These mechanisms also support the potential use of NMDA receptor antagonists once a benzodiazepine has not worked.[21–23] However, as this pathophysiological research is being done in animal models of status epilepticus, future work in patients is required to confirm the mechanisms.

Aetiology

The cause of status epilepticus is of particular importance for determining appropriate treatment and prognosis. Status epilepticus can arise from infections, vascular causes, metabolic disturbances, trauma, space-occupying lesions, genetic disorders, autoimmune disorders, iatrogenic or medication-related causes, toxic exposures, or drug withdrawal. Causes can be classified, according to the ILAE criteria, into symptomatic or cryptogenic.[5] Symptomatic status epilepticus has an identifiable cause and is further classified into acute, remote, progressive, and status epilepticus in defined electroclinical syndromes (panel 1). The heterogeneous causes of acute symptomatic status epilepticus are further classified into four subcategories: acute triggering factors in epilepsy, acute primary CNS pathology, acute secondary CNS pathology, and acute toxic causes.[24] Among these subgroups, acute primary CNS pathology (eg, CNS infection) has the highest risk of poor outcomes and in-hospital mortality. Conversely, acute triggering factors in epilepsy (eg, subtherapeutic concentrations of antiseizure medications) have the lowest risk of poor outcomes and in-hospital mortality, emphasising the importance of distinguishing these categories to tailor treatment and address prognostic differences among subgroups.[24] Additionally, a substantial proportion of cases comprise remote symptomatic causes, largely structural brain lesions.

Panel 1: Causes of status epilepticus, defined according to International League Against Epilepsy criteria[5]

Symptomatic

Symptomatic status epilepticus has an identifiable cause.

Acute

- Acute triggering factors in epilepsy (eg, withdrawal or subtherapeutic doses of antiseizure medications, febrile illness, or sleep deprivation)
- Acute primary CNS pathology (eg, cerebrovascular disease, CNS infection, or head trauma)
- Acute secondary CNS pathology (eg, metabolic disturbances, systemic infection, or fever)
- Acute toxic causes (eg, alcohol withdrawal or drug or toxin exposure)

Remote

- Post-traumatic (eg, closed, open, or penetrating head injury)
- Post-infectious (eg, acute or chronic bacterial meningitis, acute viral encephalitis, or progressive leukoencephalopathy)
- Post-stroke (eg, ischaemic stroke, intracerebral or subarachnoid bleeding, or subdural or epidural haematoma)

Progressive

- Brain tumours
- Progressive myoclonic epilepsies (eg, Unverricht–Lundborg disease and Lafora disease)
- Neurodegenerative disorders (eg, Alzheimer's disease and corticobasal degeneration)

Status epilepticus in defined electroclinical syndromes

- Tonic status epilepticus in early infantile developmental and epileptic encephalopathy, infantile epileptic spasms syndrome, and Lennox–Gastaut syndrome
- Autonomic status epilepticus in early-onset benign childhood occipital epilepsy
- Myoclonic status epilepticus in Alzheimer's disease
- Non-convulsive status epilepticus in Creutzfeldt–Jakob disease

Cryptogenic

Cryptogenic status epilepticus has an unknown cause.

Diagnosis

The differential diagnosis of convulsive status epilepticus includes movement disorders (eg, dystonia and myoclonus) and psychogenic non-epileptic seizures (also known as functional seizures),[5] so diagnostic testing needs to exclude these disorders by identifying the cause of the seizures. The diagnosis of convulsive status epilepticus is largely clinical. A comprehensive history, physical examination, appropriate laboratory and imaging studies, and EEG are paramount to identifying the underlying cause (figure 1). Laboratory studies should include, at a minimum, a complete blood count, measurement of glucose and electrolytes, and a pregnancy test in patients of childbearing potential. Additionally, renal and liver function tests, blood gas, lactate, troponin, creatine kinase, and toxicology screening should be performed, if possible. Investigations to identify treatable infectious causes include blood and urine cultures and appropriate microbiological testing, with consideration of local pathogens.[26] Elevated amounts in serum of prolactin, measured 10–20 min after a seizure event, have a sensitivity of 53% and specificity of 93% for diagnosis of status epilepticus and can help to differentiate epileptic seizures from psychogenic non-epileptic seizures.[27] However, the use of this test is limited by the ability to obtain the sample within 20 min of a seizure event. A lumbar puncture is indicated in patients with signs of meningitis, and it should be considered for those who appear severely ill or are younger than 18 months, have a prolonged complex febrile seizure, have an incomplete or unknown vaccination status (particularly for patients who are not vaccinated against *Haemophilus influenza* type b or

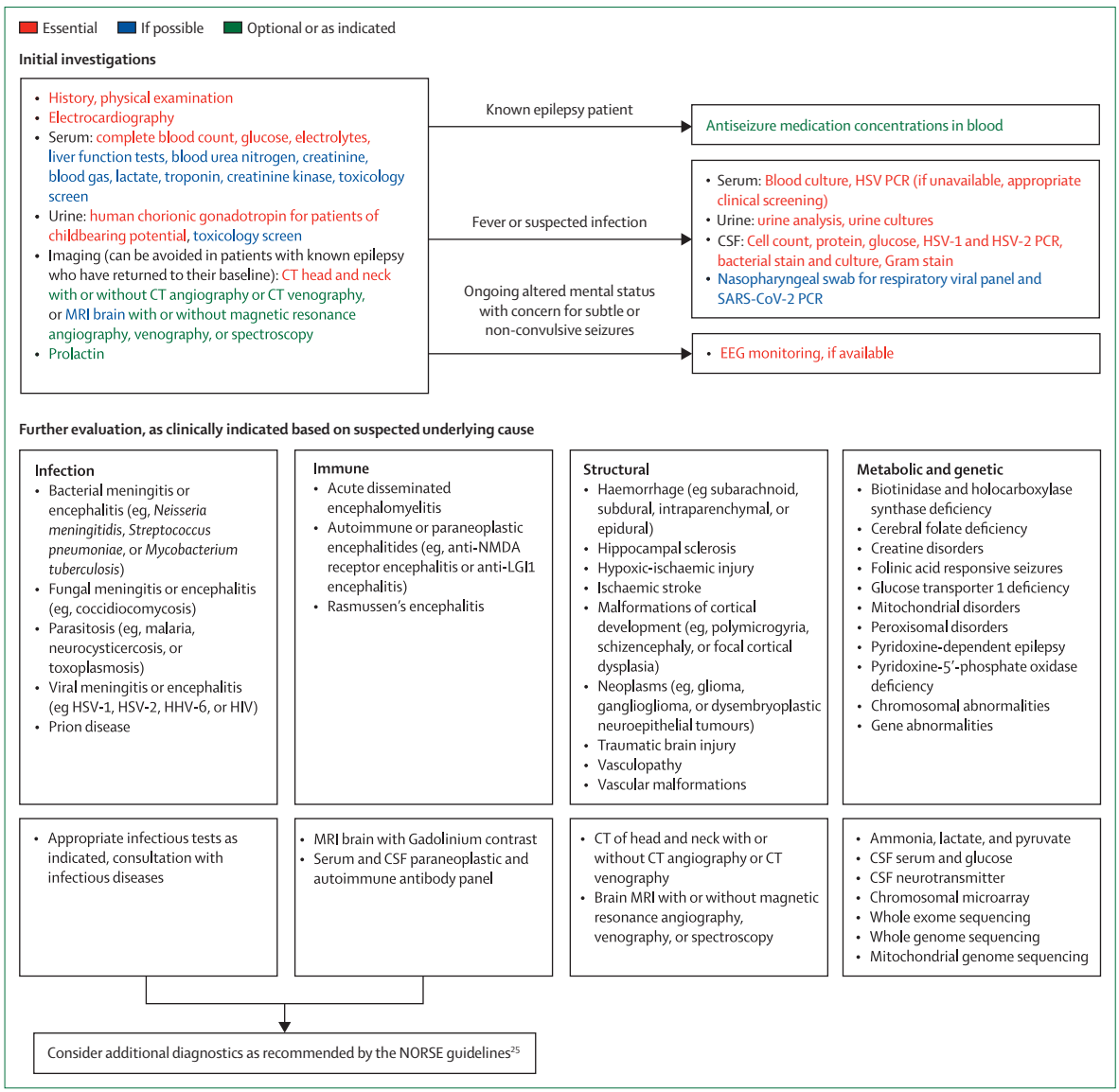
Essential
If possible
Optional or as indicated
Initial investigations
History, physical examination
Electrocardiography
Serum: complete blood count, glucose, electrolytes, liver function tests, blood urea nitrogen, creatinine, blood gas, lactate, troponin, creatinine kinase, toxicology screen
Urine: human chorionic gonadotropin for patients of childbearing potential, toxicology screen
Imaging (can be avoided in patients with known epilepsy who have returned to their baseline): CT head and neck with or without CT angiography or CT venography, or MRI brain with or without magnetic resonance angiography, venography, or spectroscopy
Prolactin
Known epilepsy patient
Antiseizure medication concentrations in blood
Fever or suspected infection
Serum: Blood culture, HSV PCR (if unavailable, appropriate clinical screening)
Urine: urine analysis, urine cultures
CSF: Cell count, protein, glucose, HSV-1 and HSV-2 PCR, bacterial stain and culture, Gram stain
Nasopharyngeal swab for respiratory viral panel and SARS-CoV-2 PCR
Ongoing altered mental status with concern for subtle or non-convulsive seizures
EEG monitoring, if available
Further evaluation, as clinically indicated based on suspected underlying cause
Infection
Bacterial meningitis or encephalitis (eg, Neisseria meningitidis, Streptococcus pneumoniae, or Mycobacterium tuberculosis)
Fungal meningitis or encephalitis (eg, coccidiocomycosis)
Parasitosis (eg, malaria, neurocysticercosis, or toxoplasmosis)
Viral meningitis or encephalitis (eg HSV-1, HSV-2, HHV-6, or HIV)
Prion disease
Immune
Acute disseminated encephalomyelitis
Autoimmune or paraneoplastic encephalitides (eg, anti-NMDA receptor encephalitis or anti-LGI1 encephalitis)
Rasmussen's encephalitis
Structural
Haemorrhage (eg subarachnoid, subdural, intraparenchymal, or epidural)
Hippocampal sclerosis
Hypoxic-ischaemic injury
Ischaemic stroke
Malformations of cortical development (eg, polymicrogyria, schizencephaly, or focal cortical dysplasia)
Neoplasms (eg, glioma, ganglioglioma, or dysembryoplastic neuroepithelial tumours)
Traumatic brain injury
Vasculopathy
Vascular malformations
Metabolic and genetic
Biotinidase and holocarboxylase synthase deficiency
Cerebral folate deficiency
Creatine disorders
Folinic acid responsive seizures
Glucose transporter 1 deficiency
Mitochondrial disorders
Peroxisomal disorders
Pyridoxine-dependent epilepsy
Pyridoxine-5′-phosphate oxidase deficiency
Chromosomal abnormalities
Gene abnormalities
Appropriate infectious tests as indicated, consultation with infectious diseases
MRI brain with Gadolinium contrast
Serum and CSF paraneoplastic and autoimmune antibody panel
CT of head and neck with or without CT angiography or CT venography
Brain MRI with or without magnetic resonance angiography, venography, or spectroscopy
Ammonia, lactate, and pyruvate
CSF serum and glucose
CSF neurotransmitter
Chromosomal microarray
Whole exome sequencing
Whole genome sequencing
Mitochondrial genome sequencing
Consider additional diagnostics as recommended by the NORSE guidelines[25]

Figure 1: **Diagnostic evaluation for status epilepticus**
HHV=human herpes virus. HSV=human simplex virus. LGI1=leucine-rich glioma-inactivated 1. NORSE=new-onset refractory status epilepticus.

Streptococcus pneumoniae),[28] or who received antimicrobials before a clinical evaluation. The CSF profile is helpful in uncovering an infectious, inflammatory, or neoplastic cause. Elevated CSF protein might occur in patients with seizures in the absence of an identified underlying cause.[29] Historically, CSF pleocytosis was attributed to prolonged seizures.[30] However, with modern neuroimaging and laboratory investigations, an infectious or immune-mediated cause can be identified in this clinical scenario.[29,31] CSF pleocytosis must prompt more investigation and not be attributed to the direct result of the seizure. Urgent CT neuroimaging should be performed before lumbar puncture if increased intracranial pressure or a lesion that could cause herniation is possible.[32]

Although convulsive seizures are easily identifiable, seizures can often begin or continue, particularly after treatment, with minimal or no clinical manifestations. These seizures are referred to as non-convulsive, subclinical, or electrographic-only seizures. Patients with non-convulsive seizures can also present with confusion, lethargy, agitation, delirium, and speech disturbances. EEG monitoring can be helpful in patients who do not return to their baseline consciousness, in whom there is a concern for ongoing non-convulsive seizures, or in the setting of neuromuscular blockade or sedation that limits clinical assessment for seizures (figure 1). Approximately half of patients with ongoing alterations in consciousness after status epilepticus might show continued non-convulsive seizures on EEG.[33] Situations that predict a

high risk of non-convulsive seizures are admission to the neurointensive care unit, particularly when receiving neurotoxic medications (eg, cephalosporins, ifosfamide, methotrexate, ketorolac, baclofen, lithium, opioids, and opioid antagonists), previous epilepsy diagnosis, a preceding generalised tonic-clonic seizure, female sex, and history of head injury and stroke.[34,35] In patients with known epilepsy who return to baseline without concern for ongoing subclinical seizures, EEG monitoring might not be needed.

Limitations of EEG for monitoring of subclinical seizures are that interpretation and reporting rely on the labour-intensive visual analysis of digital EEG data by highly trained electroencephalographers. Moreover, continuous EEG with simultaneous video recording is resource-intensive and is not available in all centres, particularly those in LMICs. In settings where continuous EEG is unavailable, intermittent routine EEGs could be used;[36,37] however, in a quality improvement study, this strategy missed at least 10% of subclinical seizures.[38] Although intermittent EEGs can reduce the time needed for interpretation by the electroencephalographer, placing and replacing the EEG electrodes is not necessarily less resource-intensive for EEG technologists. An alternative strategy relies on computational analysis and automated seizure detection algorithms to reduce clinician workload. Quantitative EEG software displays large amounts of EEG data acquired over hours or days, in trends, allowing for fast analysis and for the detection of gradual changes occurring over time. However, these findings necessitate additional confirmatory review of the raw EEG data, and quantitative EEG detection of seizures is subject to false positive findings, often due to artifacts. In a prospective observational study, bedside providers screened quantitative EEG trends for seizures, with high sensitivity but low specificity.[39] A consequence of low specificity is potential overtreatment with antiseizure medications.

Technologies are emerging that reduce the time and resources required for EEG application and interpretation, including reduced electrode montages, caps, and bands, which can serve as screening tools to guide whether patients require conventional EEG monitoring.[40] However, these technologies might play a more prominent role in settings with little access to conventional EEG. In Bhutan, a smartphone and tablet-based EEG app in combination with 14-electrode caps was tested as an alternative to traditional EEG systems.[41] Findings showed the app was safe, affordable, accessible, and portable when compared with standard EEG recordings, and sensitivity for the detection of epileptiform discharges was 39% and specificity was 95%.[41]

Management

Initial management of status epilepticus requires stabilisation of the patient and concurrent evaluation for reversible causes. If rapid sequence intubation is required for respiratory distress, ketamine or propofol can be used, as they have antiseizure properties. Starting the treatment with a rapidly acting benzodiazepine within the first 5–10 min of seizure onset (after t_1) is essential.[42,43] If the seizure persists 5–10 min after the first benzodiazepine dose, a second dose should be administered. Emergency providers must take into account any doses administered before hospital arrival. A delay in treatment in the magnitude of minutes increases the risks of prolonged status epilepticus.

Due to their safety and efficacy, benzodiazepines are the first-line treatment for status epilepticus.[44] In animal studies, when administered as early as 15 min after

Stabilisation and resuscitation
Treatment steps in adults and children
Side-effects
First-line
Intravenous or intraosseous access
• Diazepam 0·2 mg/kg intravenous, intraosseous (maximum 10 mg)
• Lorazepam 0·1 mg/kg intravenous, intraosseous (maximum 4 mg)
No Intravenous or intraosseous access
• Diazepam 5–15 mg buccal, 50–20 mg intranasal, 0·2–0·5 mg/kg rectal (maximum 20 mg)
• Lorazepam 0·1 mg/kg buccal (maximum 4 mg)
• Midazolam 0·3–0·5 mg/kg buccal, 0·2 mg/kg intranasal, intramuscular (maximum 10 mg)
Second-line
• Fosphenytoin 20 mg phenytoin equivalents per kg intramuscular, intravenous, intraosseous (maximum 1500 mg phenytoin equivalents)
• Levetiracetam 40–60 mg/kg intravenous, intraosseous (maximum 4500 mg)
• Phenobarbital 15–20 mg/kg intravenous, intraosseous (maximum 1000 mg)
• Phenytoin* 20 mg/kg intravenous, intraosseous (maximum 1500 mg)
• Valproic acid 20–40 mg/kg intravenous, intraosseous (maximum 3000 mg)
Third-line
• Ketamine 0·5–3 mg/kg intravenous loading dose, then 1·5–10 mg/kg per hour continuous infusion
• Midazolam 0·2 mg/kg intravenous loading dose, then 0·05–2 mg/kg per hour continuous infusion
• Pentobarbital 5 mg/kg intravenous loading dose, then 0·5–5 mg/kg per hour continuous infusion
• Propofol 1-2 mg/kg intravenous loading dose, then 20–200 mcg/kg per minute continuous infusion
• Thiopental 1–5 mg/kg intravenous loading dose, then 0·5–5 mg/kg per hour continuous infusion
• If available, continuous video EEG should be used to guide treatment
• Benzodiazepine: respiratory depression, sedation
• Fosphenytoin: arrhythmia, hypotension, possible worsening of seizures due to toxins that also block sodium channels, possible worsening of seizures in patients with Dravet syndrome
• Phenobarbital: respiratory depression, apnoea, hypotension
• Phenytoin: infusion site reaction, arrhythmia,hypotension, possible worsening of seizures due to toxins that also block sodium channels, possible worsening of seizures in patients with Dravet syndrome
• Levetiracetam: mood changes
• Valproic acid: hepatotoxicity, thrombocytopenia
• Ketamine: hypertension, supraventricular tachycardia, metabolic acidosis
• Pentobarbital: respiratory depression, hypotension, cardiac depression, ileus
• Propofol: respiratory depression, hypotension, cardiac failure, propofol infusion syndrome, rhabdomyolysis, renal failure, metabolic acidosis, risk of propofol infusion syndrome (particularly in children)
• Thiopental: respiratory depression, hypotension, cardiac depression
Considerations for low-income and middle-income countries:
• If intravenous antiseizure medication is not available, consider:
• Levetiracetam 40 mg/kg via nasogastric tube (max dose 4500 mg)
• Phenobarbital 15–20 mg/kg intramuscular (max dose 1000 mg)
• If continuous monitoring or intervention for hypotension or respiratory depression is not available:
• Levetiracetam is preferred due to decreased risk of sedation, hypotension, and respiratory depression
• Loading doses of antiseizure medication can be divided and administered more slowly
• Small doses of ketamine can be used without the need for mechanical ventilation

Figure 2: **Treatment algorithm for convulsive status epilepticus including medication adverse events and considerations for low-income and middle-income countries**[11]

*Fosphenytoin is a pro-drug of phenytoin with a higher molecular weight than phenytoin. Thus, fosphenytoin is dosed in phenytoin equivalents to avoid confusion.

onset of seizures, benzodiazepines have sometimes not terminated status epilepticus due to pharmacoresistance, but a study of the effectiveness of diazepam showed that the cause of the seizures could determine whether benzodiazepine pharmacoresistance will occur.[45] Yet, patients in status epilepticus can remain responsive to benzodiazepines after 15 min.[46,47] For these reasons, even for prolonged status epilepticus, treatment should begin with a benzodiazepine, rapidly followed by a second-line agent if needed, to avoid delays in the transition from benzodiazepines to non-benzodiazepine treatments.[19,21–23,45]

Benzodiazepine availability varies worldwide, which affects the optimal first-line treatment choice.[44,48–51] The most common recommended first-line benzodiazepines are diazepam, lorazepam, and midazolam (figure 2). Systematic reviews indicate that if clinicians have access to all benzodiazepines, they prefer lorazepam over diazepam in both adults and children.[51,52] Diazepam is more commonly available globally[53] because it is more affordable than midazolam and lorazepam and can be stored at room temperature. Midazolam can also be stored at room temperature. Lorazepam is heat-sensitive and requires refrigeration to 2–8°C, which adds to the cost of storage.[54,55] Rectal diazepam is widely available globally, although it is still unavailable in 40% of low-income countries (LICs), potentially due to cost, supply chain issues, or insufficient awareness or training. Buccal midazolam is available in more than half of LICs, but specific access might vary based on sources of medications and rural or urban locations. Among intravenous benzodiazepines, intravenous diazepam is widely available, whereas intravenous midazolam is available in approximately 30% of LICs, and intravenous lorazepam is available in less than 22% of LICs.[56] Although intravenous administration is preferred when feasible, it requires trained staff and equipment. Prepackaged intranasal benzodiazepines are rarely available in many countries.[56]

When benzodiazepines are unavailable, intravenous or intramuscular phenobarbital can be used as a first-line treatment.[57] In LMICs, providing optimal medication dosing with a risk of respiratory depression in the absence of continuous monitoring or haemodynamic and ventilatory support can be challenging.[44] In these situations, loading doses can be divided and administered cautiously in two doses. Levetiracetam via nasogastric tube is another option: a study comparing enteral levetiracetam with enteral phenobarbital in convulsive seizure management during cerebral malaria showed equivalent efficacy to phenobarbital and a lower risk of hypotension and respiratory depression.[58]

Second-line treatment consists of non-benzodiazepine antiseizure medications (figure 2). Guidelines from the Neurocritical Care Society and American Epilepsy Society include recommendations for administering fosphenytoin, valproate, levetiracetam, and phenobarbital[57] within 20–40 min of status epilepticus onset. The Established Status Epilepticus Treatment Trial (ESETT) evaluated valproic acid, levetiracetam, and fosphenytoin.[3] The Convulsive SE Pediatric Trial (ConSEPT)[1] and Emergency Treatment with Levetiracetam or Phenytoin in Status Epilepticus in children (EcLIPSE)[2] trials both compared levetiracetam with phenytoin. In these randomised trials, no difference in efficacy was found between the agents tested, and the response was similar when stratified by age.[59] In the Treatment of Recurrent Electrographic Non-convulsive Seizures (TRENdS) randomised trial, lacosamide was found to be non-inferior to fosphenytoin.[60] Lacosamide and phenobarbital have been evaluated in additional longitudinal series and meta-analyses,[61] none of which found a compelling difference in the type of second-line agent. Evidence for new medications with intravenous formulations (eg, lacosamide and brivaracetam) is insufficient.

The choice of first-line or second-line agent is only one aspect of status epilepticus management, and the role of training, route of administration, and treatment algorithms cannot be ignored. A quality improvement study showed that the implementation of acute status epilepticus treatment algorithms in an inpatient setting resulted in a decrease in ICU transfers from 39% to 9%.[62] Another quasiexperimental cohort study of a status epilepticus alert protocol reduced the time to administration of a second-line antiseizure medication from 58 min to 22 min.[63]

No large randomised controlled trials have been conducted to guide the optimal choice or dose of medication for the management of refractory or super-refractory status epilepticus. Treatment is dictated by the underlying cause, rational polypharmacy to target different mechanisms of action, pharmacokinetics, drug–drug interactions, and mitigating side-effects in a critically ill patient. If first-line and second-line medications do not terminate status epilepticus, a continuous infusion of midazolam, propofol, or pentobarbital should be considered (figure 2). In observational studies comparing midazolam, pentobarbital, and propofol in patients with refractory status epilepticus, there was an association between pentobarbital treatment and greater seizure suppression but an increased risk of hypotension.[63,64] Over the past few decades, trends have been to use propofol or midazolam rather than barbiturates. However, prolonged sedation with propofol increases the risk of propofol infusion syndrome (characterised by potentially lethal metabolic acidosis, hyperkalaemia, hypertriglyceridaemia, rhabdomyolysis, transaminitis, renal failure, and arrhythmias), particularly in children, in which the use of the medication is restricted to less than 24–48 h. Propofol is not recommended in patients with a suspected underlying mitochondrial disorder or in

patients on a concomitant ketogenic diet.[65] A randomised controlled trial in super-refractory status epilepticus of anaesthetics plus the GABA type A receptor allosteric modulator allopregnanolone, compared with standard anaesthetics, did not show efficacy.[66] Ketamine is a non-competitive NMDA receptor antagonist that can be used as an alternative to propofol, benzodiazepine, or barbiturate infusions.[67] Ketamine has a distinct mechanism of action from other commonly used antiseizure medications and does not cause haemodynamic or respiratory compromise. In settings with little capacity for mechanical ventilation, small doses of ketamine can be used.[68] Hypothermia has not been shown to confer a benefit besides standard therapies.[69]

According to an observational cohort study, treating physicians commonly treated refractory status epilepticus by titrating anaesthetic drugs under consultation of a neurologist to induce a pharmacological coma, maintain clinical and electrographic seizure suppression, and reach a burst suppression pattern on EEG. This strategy theoretically offers neuroprotection by reducing cerebral metabolic demands,[70] but it requires high doses of sedatives, which can themselves be neurotoxic and result in hypotension, respiratory depression, and prolonged coma. Inducing burst suppression has not been shown to improve mortality in retrospective observational studies of patients with status epilepticus.[71] Burst suppression is typically maintained for 24–48 h before withdrawal of anaesthetic medications is attempted. To balance the negative effects of oversedation required to reach burst suppression and the goal of neuroprotection, an alternative objective is to titrate continuous infusions to have seizure cessation. However, the method that is superior and whether rhythmic and periodic EEG patterns should be targeted are not clear.[72,73]

A long-acting antiseizure medication (eg, fosphenytoin, lacosamide, levetiracetam, phenobarbital, or valproic acid) should be added to the continuous infusion for super-refractory status epilepticus to reach adequate serum concentrations, which will help to maintain seizure control after withdrawal of the infusion. Neurophysiological signals associated with an unsuccessful anaesthetic wean in patients with refractory status epilepticus include the presence of highly epileptiform bursts and burst amplitudes of 125 mV or more.[74,75] The interburst interval length, burst length, and burst suppression ratios were not associated with the success of an anaesthetic wean in a retrospective cohort study.[76] Quantitative neurophysiological signals might have a role in predicting the success of anaesthetic weans in the future.[76]

In settings without continuous monitoring for electrographic seizures or burst suppression, one strategy is to request 20–30 min of intermittent EEG recording every 12 h (figure 2). Another strategy for when EEG is completely unavailable is to use 24–48 h of continuous infusion as a practical cutoff for the duration of therapy. Complications can arise from ongoing seizures and prolonged exposure to continuous infusions, including haemodynamic instability, infection, blood dyscrasias, coagulopathy, metabolic derangements, and kidney and liver injury, which in turn contribute to prolonged hospitalisations, morbidity, and mortality. Hence, there is considerable interest in using non-anaesthetic therapies early during refractory status epilepticus.

If an immune-mediated cause of status epilepticus is suspected, treatment with immunotherapy is recommended within 72 h of onset.[25] The use of pulse-dose intravenous corticosteroids or intravenous immunoglobulin as first-line treatment for NORSE and FIRES is reasonably agreed on by experts.[25] Corticosteroids and a ketogenic diet are also treatment options in patients without an underlying immune-mediated cause, to target the inflammatory and immunologically mediated changes caused by seizures themselves or to target a yet unidentified immune-mediated cause. Second-line immunotherapy options include plasmapheresis, rituximab, tocilizumab, cyclophosphamide, and anakinra.

Medication availability is only one part of effective management of status epilepticus. Observational studies underscore the importance of training for status epilepticus management,[77] including adequate dosage, timing, and route of administration.[78,79] Clinicians and caregivers often delay administration or underdose benzodiazepines due to the perceived risk of respiratory depression. More than half of paediatric patients who receive benzodiazepines receive inadequate doses of benzodiazepines in both prehospital and in-hospital settings.[79,80] In a cross-sectional study of almost 2500 adults with status epilepticus, none were treated with adequate doses of first-line midazolam.[81] Benzodiazepines can cause respiratory depression in a dose-dependent manner, but the risk of respiratory depression from ongoing status epilepticus offsets the risk from appropriately-dosed first-line rescue benzodiazepines.[81] Caregivers should be trained to recognise seizures, administer first-line rescue medications (eg, rectal diazepam, buccal lorazepam, and buccal or intranasal midazolam), and recognise when to contact emergency medical services (EMS). Seizure action plans, videos, and simulations can enhance training.[82,83] Additionally, wearable seizure detection devices (eg, electromyography sensors, actigraphs, and EEG-based systems) aid in the detection of seizures and status epilepticus, particularly when patients are not supervised.[84] Ultimately, advancing first aid training courses to include status epilepticus treatment algorithms, similar to training for stroke and cardiac emergencies, might improve the implementation of status epilepticus treatment algorithms outside specialised centres.

***Panel 2*: Priorities for management of status epilepticus in low-income and middle-income countries**

Pre-hospital treatment

- Provide individualised seizure action plans that include:
  - A description of the individual's epilepsy and seizure types
  - The current antiseizure medication regimen
  - Seizure precautions and any specific restrictions for the individual's safety
  - When to seek emergency medical care and when to contact the specialist managing the patient's seizures
  - The care provider's contact information
  - An emergency pathway with rescue medication and administration instructions, if available
  - Consideration of geographic challenges and rescue medication limitations
  - Early recognition of status epilepticus, including (where appropriate) safe treatment plans for clustering of seizures using available antiseizure medications and guidance on management if antiseizure medications are unavailable
- Improve rescue medication availability, especially nasal and buccal forms for ease of administration
- Decrease emergency medical services arrival times

Trained health-care professionals and resources

- Basic training on recognition and treatment of seizures with consideration for the specific resources available in the clinical setting in which the provider is working
- Standardised guidelines or protocols on status epilepticus tailored to locally available resources posted in every emergency unit
- Status epilepticus treatment that considers availability to respiratory support for safety
- Education emphasising the importance of time to treatment regarding rapid escalation of antiseizure medications, early polytherapy, or early continuous infusions during hospital management
- Training of non-specialists on basic epilepsy management and seizure action plan development
- Access to neurologists in person or via telehealth
- Access to rescue medications, consistent antiseizure medications supplies, intensive care unit facilities, and EEG monitoring for appropriate status epilepticus management

Public education and cultural factors

- Campaigns to improve awareness of seizures and seizure first aid, destigmatise epilepsy, and debunk common myths of contagion
- Education for seizure first aid among caregivers, teachers, and community leaders

Seizure detection and prediction devices

- Development of accessible and affordable seizure detection and prediction devices
- Technology that takes advantage of widespread smartphone availability globally

Disparities in care worldwide

Requesting EMS support for status epilepticus with onset outside the hospital setting is common globally.[85] EMS response times vary depending on the setting, and data are scarce regarding response times specific to status epilepticus, particularly in LMICs.[86–89] EMS arrival times for all causes of status epilepticus can range from 5·9 min (in a retrospective cohort study in the USA)[90] to 15 min (in a qualitative research study in Saudi Arabia)[91] in HICs, and from 7·6 min (in a retrospective descriptive cross-sectional study in Iran)[90] to 16·9 min (in a cross sectional study in Ghana)[92] in LMICs. These estimates do not account for the differences in response times between rural versus urban areas,[91] which limits generalisability. There is a paucity of literature on gender, racial, and socioeconomic disparities among patients with status epilepticus. Observational studies from Switzerland and the USA have suggested associations between the female sex and decreased odds for return to premorbid neurological function,[93] between low income and status epilepticus prevalence, and between high income and odds of receiving EEG monitoring.[94] Attention to vulnerable populations is needed to improve status epilepticus outcomes.

Prognosis

Benzodiazepine treatment terminates status epilepticus in approximately 70% of cases,[95] although the exact figure varies with circumstance. If the benzodiazepine does not terminate status epilepticus, treatment with the second-line medication is effective in approximately 50% of cases.[3] Recovery in these early stages is excellent; most patients have no long-term sequelae.[96]

The outcome in refractory status epilepticus is poorer than in status epilepticus. In approximately 50% of patients, morbidity includes epilepsy, cognitive impairment, and the consequences of prolonged anaesthesia and ventilation in the ICU. Estimates of the 5-year rates of seizure recurrence in adults with first-time non-hypoxic status epilepticus range from 9% for patients with acute toxic causes to 66% for patients with progressive causes.[94] Risk factors for seizure recurrence after status epilepticus are progressive causes, status epilepticus with prominent motor phenomena evolving into non-convulsive status epilepticus, and non-convulsive status epilepticus.[97] Mortality rates of 40% or more have been reported for refractory status epilepticus,[98] and in-hospital rates might underestimate the true mortality. In a retrospective cohort study from Finland, of 395 patients with refractory status epilepticus who required ICU treatment, the eventual hospital mortality rate was 7·4%, and the 1-year mortality rate was 25·4%.[15,99] Mortality was highest in patients with the longest duration of status epilepticus, the greatest degree of dependency, and patients aged 80 years or older. A meta-analysis of patients with generalised convulsive status epilepticus found a mortality

ratio of 15·9% but, disappointingly, concluded that mortality from convulsive status epilepticus had not improved over nearly three decades (1990–2017).[100] Among patients with non-hypoxic refractory status epilepticus, estimates of in-hospital mortality approached 20% in 2023.[6] Compared with patients with refractory status epilepticus who are responsive to antiseizure medications, patients with refractory status epilepticus who require general anaesthesia have three times the risk of in-hospital mortality, and patients with super-refractory status epilepticus have almost four times the risk of in-hospital mortality.[97] Mortality in paediatric status epilepticus is much lower, ranging from 3–11%.[101]

The greatest effect on mortality and morbidity is the underlying cause of status epilepticus, with the highest rates recorded in hypoxic brain injury and any other pathology that results in large-scale neuronal destruction. Among the common causes, those with acute brain injury, hypoxic–anoxic encephalopathy, and inflammatory or autoimmune disorders have especially poor outcomes. The outcome is better for people with existing epilepsy than for those with first-presentation status epilepticus. Outcomes depend on the quality of ICU care, and the longer status epilepticus remains resistant to treatment, the greater the risk of ICU complications. Several prognostic scoring systems are available to predict outcomes (eg, STESS, EMSE, and END-IT scores), which have little use in deciding on treatment approaches.[15]

Conclusions and future directions

Status epilepticus and its associated morbidity and mortality are potentially preventable. Effective treatment is crucial to control seizures and prevent refractory and super-refractory status epilepticus.[62,84] Strategies for improved outpatient care include better detection and prediction, accessible rescue medications, and seizure action plans, particularly in settings where timely access to EMS can be a barrier, such as LMICs. Key interventions in LMICs might include providing medications at the point of care, enhancing education, implementing seizure action plans, and using diagnostic tools such as mobile apps, wearables, and portable EEG systems (panel 2). A detailed hub-and-spoke network of acute neurological care centres and telemedicine approaches, akin to stroke networks, might enable prompt evaluation, treatment, and care for patients en route to advanced care centres in all settings. Future steps for research in status epilepticus include evaluating social determinants of health and disparities in care, conducting granular and extensive longitudinal follow-up studies with detailed clinical, neurophysiological, and neuropsychological outcome measures, and optimising diagnostic approaches and personalised treatment regimens, including predictive and preventive strategies. As status epilepticus care moves towards early detection, prediction, and prevention, we envision reduced health-care use, fewer emergency room visits and ICU stays, and improved morbidity and mortality in status epilepticus.

Search strategy and selection criteria

References for this review were identified by searching PubMed and Embase for articles published between Sept 4, 2015, and July 1, 2024, because 2015 was the year when the International League Against Epilepsy published the revised definition and classification of status epilepticus. The main search terms were ("Status Epilepticus" OR "status epilepticus pathophysiology" OR "status epilepticus epidemiology" OR "status epilepticus mortality") OR "antiseizure medication". We excluded papers not written in English, conference abstracts, and case reports. Google Scholar was also searched to identify unpublished data and grey literature. Additionally, we included articles identified in the reference list of relevant articles and were ultimately selected by relevance, with a preference for newer articles within the search interval. The final reference list was generated on the basis of the relevance of the search results to the topic covered in this Review.

Contributors

All authors contributed to the conceptualisation, data curation, formal analysis, investigation, methodology, writing of the original draft, and review and editing of the Review.

Declaration of interests

JVG receives research funding from the National Institutes of Health (NIH). FMAC was partly funded by the Epilepsy Research Fund. AAP receives research support from the NIH and National Institute of Neurological Disorders and Stroke (NINDS); serves on the advisory board of ROW Foundation; and is a consultant for the WHO Brain Health Unit. HPG receives salary support from the NIH and NINDS. TL receives research funding from NIH, Epilepsy Research Fund, and Epitel; received data for separate research from Sumitomo Pharma; receives travel support and speaker honoraria for Grand Rounds at academic centres and national and international meetings; is part of patent applications to detect and predict clinical outcomes and to detect, manage, diagnose, and treat neurological conditions, epilepsy, and seizures; serves as the consortium principal investigator of the Pediatric Status Epilepticus Research Group; serves on various committees and roles in national societies; and received device donations from Epitel and Empatica. While working in his laboratory, some of TL's trainees received salary support from international foundations and societies and academic centres. SS declares no competing interests.

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